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Neonatal hyperbilirubinaemia necessitating exchange transfusion due to maternal sickle cell crisis

Short title: Maternal sickle cell disease and neonatal hyperbilirubinaemia

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ABSTRACT

Background: Pregnancy in women with sickle cell disease is associated with a number of fetal complications such as intra-uterine death, intra-uterine growth restriction (IUGR), preterm birth, low birth weight and an increased perinatal mortality and morbidity. Hyperbilirubinemia necessitating exchange transfusion in an infant of a mother with sickle cell disease, to our knowledge, has not been previously described.

Highlights: An infant was delivered at 33 weeks and 5 days of gestation due to a maternal sickle cell crisis. The infant had an unconjugated bilirubin level of 153 micromols/L on admission to the neonatal intensive care unit at 30 minutes of age. Phototherapy was immediately commenced, intravenous immunoglobulin administered and then a double-volume exchange transfusion performed. There was, however, no evidence of haemolysis in the infant and the infant's haemoglobin level remained stable following the exchange. No further exchange transfusions were required. The mother had a high unconjugated bilirubin level (151 micromols/L) prior to delivery.

Conclusion: High neonatal unconjugated bilirubin levels necessitating exchange transfusion can occur due to haemolysis in the maternal circulation, in this case due to sickle cell disease.

Keywords: exchange transfusion, transplacental transfer, maternal sickle cell disease.

LIST OF ABBREVIATIONS

IUGR Intra-uterine growth restriction

LBW Low birth weight

SCD Sickle cell disease

INTRODUCTION

Severe unconjugated hyperbilirubinemia can result in kernicterus which can result in sensorineural hearing loss, dystonia and athetoid cerebral palsy. Mothers with sickle cell disease (SCD) who have an acute sickle cell crisis suffer haemolysis resulting in an increase in unconjugated bilirubin levels. Unconjugated bilirubin can transfer across placenta from the maternal to fetal circulation and vice versa, whereas it has been demonstrated in animal models, very little conjugated bilirubin is able to cross the placenta [1, 2]. Maternal bilirubin levels at delivery are comparable post-partum neonatal bilirubin levels as reported in infants born to mothers with Crigler Najjar Syndrome. Affected infants have been reported to require an exchange transfusion for severe hyperbilirubinemia.

Sickle cell disease is an autosomal recessive haemoglobinopathy and is one of the most common monogenic inherited disorders in the world. Pregnant women with sickle cell disease are at an increased risk of having obstetric and sickle related complications. Pregnant women suffer more painful crises both pre and post-partum [3], with an increased risk of anaemia, pre-eclampsia and eclampsia [4]. Acute sickle cell pain is common, occurring in between 7 and 25% of pregnancies [3]. There is a higher risk of stillbirth, intra-uterine growth restriction (IUGR), low birth weight (LBW) and premature delivery, the latter being significantly affected by sickle related events in pregnancy [5]. A systematic review of sixteen studies in pregnancy outcomes of women with SCD in low or high income countries was undertaken [6]. SCD was associated with intrauterine growth retardation odds ratio (OR) 2.79, 95% confidence intervals (CI) 1.85-4.21), perinatal mortality (OR 3.76,

95% CI 2.34-6.06) and low birth weight (OR 2.00, 95% CI 1.42-2.83). It was associated with an increased risk of pre-eclampsia (OR 2.05, 95% CI 1.83-65.11) and eclampsia (OR 3.02, 95% CI 1.20 – 7.58) [6].

We report an infant who required an exchange transfusion for severe unconjugated hyperbilirubinemia resulting from maternal haemolysis due to a sickle cell crisis.

CASE PRESENATION

A premature infant was born at 33 weeks and five days of gestation with a birthweight of 1980 grams (twenty-fifth centile for weight) to a primigravida mother with sickle cell disease (HbSS). All the ultrasound examinations of the fetus and Doppler-studies were normal, there was no evidence of fetal growth restriction. Throughout the pregnancy she had a baseline haemoglobin of 70gm/L. The mother also had glucose-6-phosphate dehydrogenase (G6PD) deficiency. She has had one episode of painful crisis at 15 weeks of gestation needing hospital admission. She had a further sickle cell crisis at 32 weeks of gestation and required an exchange transfusion, following which she developed atypical antibodies.

The infant was delivered at 33 weeks and five days of gestational age by caesarean section for maternal reasons, that is on-going sickle cell crisis and sepsis. The mother received intravenous immunoglobulin at delivery, her unconjugated bilirubin level then was 151 micromols/L. At 30 minutes of age, the infant's bilirubin level was 153 micromols/L. The infant was, therefore, immediately started on triple phototherapy and was given intravenous immunoglobulin by three

hours of age, based on the National Institute of Clinical excellence (NICE) guidelines for exchange transfusion [7]. A double volume exchange transfusion was performed at five hours of age which reduced the bilirubin level to 110 micromols/L. The packed cell volume before the exchange transfusion was 41.8%. The blood group of the infant was A positive, the maternal blood group was A positive and the Direct Antiglobulin Test (DAT) was negative. Phototherapy was continued for another 48 hours during which time there was no rebound rise in the bilirubin level. The magnetic resonance imaging scan of the brain performed at term showed no evidence of bilirubin encephalopathy. The blood cultures taken immediately after birth were negative.

DISCUSSION

We report an infant who required an exchange transfusion, but had no ongoing morbidities due to jaundice. The mother had SCD and we suggest that the neonatal hyperbilirubinaemia was due to maternal haemolysis resulting in an elevated bilirubin level in the maternal circulation immediately prior to delivery. Our theory is supported by the lack of other causes of early neonatal jaundice and, following the exchange transfusion, there was no increase in bilirubin levels.

Approximately 100-200 women with SCD become pregnant each year in the UK [3]. Pregnant women with SCD experience increased morbidity mainly due to sickle related crises and in fewer cases due to venous thromboembolism, infection and chronic end organ dysfunction. The processes contributing to increased maternal

complications are pregnancy induced hypertension (PIH), painful crises, antepartum haemorrhage, eclampsia, placenta praevia and pulmonary problems; there is also an increased maternal mortality. Complications are more common in women with an HbSS rather than a HbSC phenotype. In our report, the mother had HbSS phenotype and was anaemic during the pregnancy. Women with SCD are six times more likely to deliver prematurely than the general population [4] and there is also higher incidence of caesarean delivery in pregnant women with SCD. In this case, the infant was born prematurely at 33 weeks and five days of gestation by an emergency caesarean section for maternal sickle crisis and suspected sepsis.

Mothers with SCD are more likely to give birth to infants who have suffered intrauterine growth retardation (IUGR), partly due to underlying hypertension and placental insufficiency [6]. Growth restriction in utero also results from sickling and vaso-occlusion in the placental circulation, with increased blood viscosity affecting perfusion of the placenta and a reduced oxygen content in the blood due to chronic maternal anaemia. The infant currently presented was delivered prematurely and their birth weight was on the twenty-fifth percentile for length.

The infant was noted to be jaundiced soon after birth with an unconjugated bilirubin level of 153 micromols/L at 30 minutes of age, which reflected the maternal unconjugated bilirubin level. The fetal liver has low uridine-diphosphate glucuronosyltransferase 1A1 enzyme activity and hence the fetus is dependent on transfer of unconjugated bilirubin across the placenta into maternal circulation where it is converted to conjugated bilirubin and excreted by the maternal liver. The transfer of bilirubin from the fetal to the maternal circulation occurs by passive diffusion as well as carrier mediated transfer. Bilirubin glucuronides do not

cross the placenta whereas, in contrast, unconjugated bilirubin is readily transferred from mother to the fetus in maternal conditions such as Criigler-Najjar Sydrome. Previous reports have shown almost similar plasma concentrations of unconjugated bilirubin in the infant and mother.

Prolonged bilirubin exposure of the fetus can occur in mothers with Criigler Najjar syndrome. The fetus is more susceptible to neurotoxicity from high levels of unconjugated bilirubin due to the lower binding affinity of α-fetoprotein to unconjugated bilirubin than adults [8]. The adverse outcome can be prevented by daily phototherapy with or without semi-monthly albumin transfusions in Criigler Najjar type 1 and phenobarbitone administration in mothers with Criigler Najjar type 2. In pregnant women with SCD, no specific interventions to reduce bilirubin have been reported, except for the management of an acute episode of sickle crisis to reduce haemolysis and further bilirubin production.

One study reported that 77.2% of infants born to mothers who had SS phenotype had neonatal jaundice, that is a two to three times higher risk of neonatal jaundice when compared to SCD infants born to mothers with a non SS phenotype [9]. The haemoglobin phenotype of infants born with SCD did not increase the adverse birth outcomes and was comparable to the infants born without SCD, but the maternal phenotype was a strong risk factor for adverse outcomes. In contrast, in a case control study of infants with SCD, each were matched with two neonates without SCD born in the same year. The SCD infants did not show increased rates of jaundice compared to those mothers without SCD [10]. The mother of our infant

had HbSS and complications during pregnancy which resulted in an elevated unconjugated bilirubin level.

Magnetic resonance imaging of the brain did not demonstrate the infant described had suffered kernicterus. Nevertheless, a spectrum of minor neurological manifestations, consistent with neuroanatomical reports and collectively termed as a "syndrome of bilirubin-induced neurologic dysfunction (BIND) can occur in the absence of classical kernicterus [1]. Those abnormalities occurred in the following domains: neuromotor signs, muscle tone abnormalities, hyperexcitable neonatal reflexes, neurobehavioural manifestations, speech and language abnormalities and sensorineural audiology and visuomotor dysfunctions [1]. These may manifest from neonatal age to childhood. Hence, our patient requires careful follow up.

In conclusion, neonatal hyperbilirubinaemia necessitating an exchange transfusion can occur in an infant of a mother with HbSS disease. Women with SCD need to be aware of this possible complication and unconjugated bilirubin levels need to be carefully monitored in the antenatal and perinatal period.

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